

DOCKET NO.: ISPT-1010/PTS-0070.P1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Donna T. Ward, et al.

Application No.: 10/719,370

Filing Date: November 21, 2003

For: MODULATION OF HIF1 $\alpha$  and HIF2 $\alpha$  EXPRESSION

Confirmation No.: Not Yet Assigned

Group Art Unit: Not Yet Assigned

Examiner: Not Yet Assigned

DATE OF DEPOSIT: *January 14, 2004*

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID, ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE UNITED STATES PATENT AND TRADEMARK OFFICE, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

*Elizabeth A. McLoud*

TYPED NAME: Elizabeth A. McLoud

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

- ☒ In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

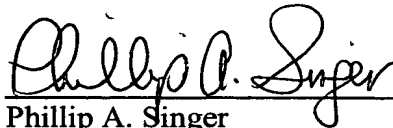
- ☐ In accordance with § 1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:
- ☐ Certification in Accordance with § 1.97(e) is attached; or
- ☐ The fee of **\$180.00** as set forth in § 1.17(p) is attached.
- ☐ In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:
- ☐ Certification in Accordance with § 1.97(e) is attached; or
- ☐ The fee of **\$180.00** as set forth in § 1.17(p) is attached.
- ☐ In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **\$180.00** as set forth in § 1.17(p).
- ☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.
- ☒ Copies of references listed on the attached Form PTO-1449 are enclosed herewith EXCEPT THAT:
- ☒ Copies of references **58-61** listed on the attached Form PTO 1449 are not required to be submitted pursuant to the June 30, 2003 recent revisions to 37 CFR § 1.98(a)(2)(i).

- ☐ In view of the voluminous nature of references [list as appropriate], and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☒ In accordance with § 1.98(d), copies of the following references listed on the attached Form PTO-1449 are not enclosed herewith because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application(s) for which a claim for priority under 35 U.S.C. § 120 have been made in the instant application:
- ☒ Copies of references **1-22** and **57** listed on the attached Form PTO-1449 were previously cited by or submitted to the Patent and Trademark Office in prior Application No. **10/304,126**, filed **November 23, 2002**.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050. This form is submitted in duplicate.

- ☐ The relevance of those listed references which are not in the English language is as follows:
- ☒ There are no listed references which are not in the English language.

Date: *January 14, 2004*

  
Phillip A. Singer  
Registration No. 40,176

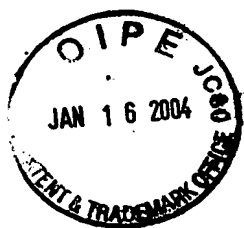
WOODCOCK WASHBURN LLP  
One Liberty Place - 46th Floor  
Philadelphia, PA 19103  
Telephone: (215) 568-3100  
Facsimile: (215) 568-3439



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office	<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
	<b>Applicant</b> Donna T. Ward, et al.	
	<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
	<b>Confirmation No.</b> Not Yet Assigned	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>		
1	Andrew, A.S. et al., "Nickel requires hypoxia-inducible factor-1 $\alpha$ , not redox signaling, to induce plasminogen activator inhibitor-1," <i>Am. J. Physiol. Lung Cell Mol. Physiol.</i> , <b>2001</b> , 281, L607-L615	
2	Caniggia, I. et al., "Hypoxia-inducible factor-1 mediates the biological effects of oxygen on human trophoblast differentiation through TGF $\beta$ <sub>3</sub> ," <i>J. Clin. Investigation</i> , <b>2000</b> , 105(5), 577-587	
3	Caniggia, I. et al., "Oxygen and Placental Development During the First Trimester: Implications for the Pathophysiology of Pre-eclampsia," <i>Placenta</i> , <b>2000</b> , 21 Suppl. A, 14, S25-S30	
4	Drutel, G. et al., "Two splice variants of the hypoxia-inducible factor HIF-1 $\alpha$ as potential dimerization partners of ARNT2 in neurons," <i>European N. Neurosc.</i> , <b>2000</b> , 12, 3701-3708	
5	Furuta, G.T. et al., "Hypoxia-inducible Factor 1-dependent Induction of Intestinal Trefoil Factor Protects Barrier Function during Hypoxia," <i>J. Exp. Med.</i> , <b>2001</b> , 193(9), 1027-1034	
6	Huang, L.E., et al., "Regulation of hypoxia-inducible factor 1 $\alpha$ is mediated by an O <sub>2</sub> -dependent degradation domain via the ubiquitin-proteasome pathway," <i>Proc. Natl. Acad. Sci. USA</i> , <b>1998</b> , 95, 7987-7992	
7	Iyer, N.V. et al., "Cellular and developmental control of O <sub>2</sub> homeostasis by hypoxia-inducible factor 1 $\alpha$ ," <i>Genes &amp; Development</i> , <b>1998</b> , 12, 149-162	
8	Kakinuma, Y. et al., "Novel Molecular Mechanism of Increased Myocardial Endothelin-1 Expression in the Failing Heart Involving the Transcriptional Factor Hypoxia-Inducible Factor-1 $\alpha$ Induced for Impaired Myocardial Energy Metabolism," <i>Circulation</i> , <b>2001</b> , 103, 2387-2394	
9	Maxwell et al., "Insights into the role of the von Hippel-Lindau gene product. A key player in hypoxic regulation," <i>Exp. Nephrol.</i> , <b>2001</b> , 9, 235-240	
10	Minchenko, A. et al., "Hypoxia-inducible factor-1 (HIF-1) mediated expression of the 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) gene: its possible role in the Warburg effect," <i>J. Biol. Chem.</i> , <b>2001</b> , 14, 21 pages	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
		<b>Applicant</b> Donna T. Ward, et al.	
		<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
		<b>Confirmation No.</b> Not Yet Assigned	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	11	Narravula, S. et al., "Hypoxia-Inducible Factor 1-Mediated Inhibition of Peroxisome Proliferator-Activated Receptor $\alpha$ Expression During Hypoxia," <i>J. Immunol.</i> , <b>2001</b> , 166, 7543-7548	
	12	Ravi, R. et al., "Regulation of tumor angiogenesis by p53-induced degradation of hypoxia-inducible factor 1 $\alpha$ ," <i>Genes &amp; Development</i> , <b>2000</b> , 14, 43-44	
	13	Ryan, H.E. et al., "HIF-1 $\alpha$ is required for solid tumor formation and embryonic vascularization," <i>EMBO J.</i> , <b>1998</b> , 17(11), 3005-3015	
	14	Semenza, G.L., "HIF-1 and human disease: one highly involved factor," <i>Genes &amp; Development</i> , <b>2000</b> , 14, 1983-1991	
	15	Semenza, G.L., "Hypoxia-Inducible Factor 1: Control of Oxygen Homeostasis in Health and Disease," <i>Pediatr. Res.</i> , <b>2001</b> , 49(5), 614-617	
	16	Sun, X. et al., "Gene transfer of antisense hypoxia inducible factor-1 $\alpha$ enhances the therapeutic efficacy of cancer immunotherapy," <i>Gene Therapy</i> , <b>2001</b> , 8, 638-645	
	17	Sutter, C.H. et al., "Hypoxia-inducible factor 1 $\alpha$ protein expression is controlled by oxygen-regulated ubiquitination that is disrupted by deletions and missense mutations," <i>Proc. Natl. Acad. Sci. USA</i> , <b>2000</b> , 97(9), 4748-4753	
	18	Thrash-Bingham, C.A. et al., "aHIF: a Natural Antisense Transcript Overexpressed in Human Renal Cancer and During Hypoxia," <i>J. Natl. Cancer Inst.</i> , <b>1999</b> , 91(2), 143-151	
	19	Wang, G.L. et al., "Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O <sub>2</sub> tension," <i>Proc. Natl. Acad. Sci. USA</i> , <b>1995</b> , 92, 5510-5514	
	20	Wang, G.L. et al., "Purification and Characterization of Hypoxia-inducible Factor 1," <i>J. Biol. Chem.</i> , <b>1995</b> , 270(3), 1230-1237	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>	



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
		<b>Applicant</b> Donna T. Ward, et al.	
		<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
		<b>Confirmation No.</b> Not Yet Assigned	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	21	Yu, A.Y. et al., "Impaired physiological responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1 $\alpha$ ," <i>J. Clin. Investigation</i> , <b>1999</b> , 103(5), 691-696	
	22	Zagzag, D. et al., "Expression of Hypoxia-Inducible Factor 1 $\alpha$ in Brain Tumors," <i>Cancer</i> , <b>2000</b> , 88(11), 2606-2618	
	23	Cockman, M.E. et al., "Hypoxia Inducible Factor- $\alpha$ Binding and Ubiquitylation by the von Hippel-Lindau Tumor Suppressor Protein," <i>J. Biol. Chem.</i> , <b>2000</b> , 275(33), 25733-25741	
	24	Conrad, P.W. et al., "The molecular basis of O <sub>2</sub> -sensing and hypoxia tolerance in pheochromocytoma cells," <i>Comparative Biochem. Physiol.</i> , <b>2001</b> , Part B, 128, 187-204	
	25	Conrad, W.P. et al., "EPAS1 <i>trans</i> -Activation during Hypoxia Requires p42/p44 MAPK," <i>J. Biol. Chem.</i> , <b>1999</b> , 274(47), 33709-33713	
	26	Ema, M. et al., "A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1 $\alpha$ regulates the <i>VEGF</i> expression and is potentially involved in lung and vascular development," <i>Proc. Natl. Acad. Sci. USA</i> , <b>1997</b> , 94, 4273-4278	
	27	Favier, J. et al., "Angiogenesis and Vascular Architecture in Pheochromocytomas," <i>Am. J. Pathology</i> , <b>2002</b> , 161(4), 1235-1246	
	28	Flamme, I. et al., "Up-Regulation of Vascular Endothelial Growth Factor in Stromal Cells of Hemangioblastomas is Correlated with Up-Regulation of the Transcription Factor HRF/HIF-2 $\alpha$ ," <i>Am. J. Pathology</i> , <b>1998</b> , 153(1), 25-29	
	29	Flamme, I. et al., "HRF, a putative basic helix-loop-helix-PAS-domain transcription factor is closely related to hypoxia-inducible factor-1 $\alpha$ and developmentally expressed in blood vessels," <i>Mechan. Develop.</i> , <b>1997</b> , 63, 51-60	
	30	Giatromanolaki, A. et al., "Relation of hypoxia inducible factor 1 $\alpha$ and 2 $\alpha$ in operable non-small cell lung cancer to angiogenic/molecular profile of tumours and survival," <i>British J. Cancer</i> , <b>2001</b> , 85(6), 881-890	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>	



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office	<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
	<b>Applicant</b> Donna T. Ward, et al.	
	<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
	<b>Confirmation No.</b> Not Yet Assigned	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>		
31	Giatromanolaki, A. et al., "Hypoxia inducible factor 1 $\alpha$ and 2 $\alpha$ overexpression in inflammatory bowel disease," <i>J. Clin. Pathol.</i> , <b>2003</b> , 56, 209-213	
32	Harris, A.L., "Hypoxia – A Key Regulatory Factor in Tumour Growth," <i>Nature Reviews</i> , <b>2002</b> , 2, 38-47	
33	Hirsila, M. et al., "Characterization of the Human Prolyl 4-Hydroxylases That Modify the Hypoxia-inducible Factor," <i>J. Biol. Chem.</i> , <b>2003</b> , 278(33), 30772-30780	
34	Hogenesch, J.B. et al., "Characterization of a Subset of the Basic-Helix-Loop-Helix-PAS Superfamily That Interacts with Components of the Dioxin Signaling Pathway," <i>J. Biol. Chem.</i> , <b>1997</b> , 272(13), 8581-8593	
35	Koukourakis, M.I. et al., "Hypoxia-Inducible Factor (HIF1A and HIF2A), Angiogenesis, and Chemoradiotherapy Outcome of Squamous Cell Head-and-Neck Cancer," <i>Int. J. Radiation Oncology Biol. Phys.</i> , <b>2002</b> , 53(5), 1192-1202	
36	Leek, R.D. et al., "Relation of Hypoxia-inducible Factor-2 $\alpha$ (HIF-2 $\alpha$ ) Expression in Tumor-infiltrative Macrophages to Tumor Angiogenesis and the Oxidative Thymidine Phosphorylase Pathway in Human Breast Cancer," <i>Cancer Res.</i> , <b>2002</b> , 62, 1326-1329	
37	Liang, Y et al., "Activation of Vascular Endothelial Growth Factor A Transcription in Tumorigenic Glioblastoma Cell Lines by an Enhancer with Cell Type-specific DNase I Accessibility," <i>J. Biol. Chem.</i> , <b>2002</b> , 277(22), 20087-20094	
38	Liu, M.Y., "Up-Regulation of Hypoxia-inducible Factor 2 $\alpha$ in Renal Cell Carcinoma Associated with Loss of Tsc-2 Tumor Suppressor Gene," <i>Cancer Res.</i> , <b>2003</b> , 63, 2675-2680	
39	Maemura, K. et al., "Generation of a Dominant-negative Mutant of Endothelial PAS Domain Protein 1 by Deletion of a Potent C-terminal Transactivation Domain," <i>J. Biol. Chem.</i> , <b>1999</b> , 274(44), 31565-31570	
40	Maxwell, P.H., "Activation of the HIF pathway in cancer," <i>Curr. Opin. Genetics &amp; Develop.</i> , <b>2001</b> , 11, 293-299	
41	Maxwell, P.H., "The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis," <i>Nature</i> , <b>1999</b> , 399, 271-275	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>

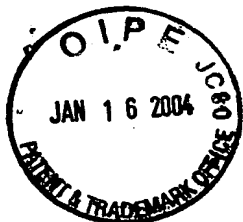


<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		<b>Docket No.</b> <b>ISPT-1010/</b> <b>PTS-0070.P1</b>	<b>Application No.</b> <b>10/719,370</b>
		<b>Applicant</b> <b>Donna T. Ward, et al.</b>	
		<b>Filing Date</b> <b>November 21, 2003</b>	<b>Group</b> <b>Not Yet Assigned</b>
		<b>Confirmation No.</b> <b>Not Yet Assigned</b>	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	42	Ohh, M. et al., "Ubiquitination of hypoxia-inducible factor requires direct binding to the $\beta$ -domain of the von Hippel-Lindau protein," <i>Nature Cell Biology</i> , <b>2000</b> , 2, 423-427	
	43	Pugh, C.W. et al., "The von Hippel-Lindau tumor suppressor, hypoxia-inducible factor-1 (HIF-1) degradation, and cancer pathogenesis," <i>Seminars in Cancer Biol.</i> , <b>2003</b> , 13, 83-89	
	44	Rajakumar, A. et al., "Expression, Ontogeny, and Regulation of Hypoxia-Inducible Transcription Factors in the Human Placenta," <i>Biol. Reproduction</i> , <b>2000</b> , 63, 559-569	
	45	Rajakumar, A. et al., "Selective Overexpression of the Hypoxia-Inducible Transcription Factor, HIF-2 $\alpha$ , in Placentas from Women with Preeclampsia," <i>Biol. Reproduction</i> , <b>2001</b> , 64, 499-506	
	46	Safran, M. et al., "HIF hydroxylation and the mammalian oxygen-sensing pathway," <i>J. Clin. Investigation</i> , <b>2003</b> , 111(6), 779-783	
	47	Sato, M. et al., "Inducible Expression of Endothelial PAS Domain Protein-1 by Hypoxia in Human Lung Adenocarcinoma A549 Cells: Role of Src Family Kinases-dependent Pathway," <i>Am. J. Respir. Cell Mol. Biol.</i> , <b>2002</b> , 26, 127-134	
	48	Semenza, G.L., "Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology," <i>Trends in Mol. Med.</i> , <b>2001</b> , 7(8), 345-350	
	49	Sowter, H.M. et al., "Predominant Role of Hypoxia-Inducible Transcription Factor (Hif)-1 $\alpha$ versus Hif-2 $\alpha$ in Regulation of the Transcriptional Response to Hypoxia," <i>Cancer Res</i> , <b>2003</b> , 63, 6130-6134	
	50	Talks, K.L. et al., "The Expression and Distribution of the Hypoxia-Inducible Factors HIF-1 $\alpha$ and HIF-2 $\alpha$ in Normal Human Tissues, Cancers, and Tumor-Associated Macrophages," <i>Am. J. Pathology</i> , <b>2000</b> , 157(2), 411-421	
	51	Tanaka, T. et al., "Endothelial PAS Domain Protein 1 (EPAS1) Induces Adrenomedullin Gene Expression in Cardiac Myocytes: Role of EPAS1 in an Inflammatory Response in Cardiac Myocytes," <i>J. Mol. Cell Cardiol.</i> , <b>2002</b> , 34, 739-748	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>	





<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
		<b>Applicant</b> Donna T. Ward, et al.	
		<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
		<b>Confirmation No.</b> Not Yet Assigned	
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	52	Tian, H. et al., "Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells," <i>Genes &amp; Development</i> , <b>1997</b> , <i>11</i> , 72-82	
	53	Tian, H. et al., "The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development," <i>Genes &amp; Development</i> , <b>1998</b> , <i>12</i> , 3320-3324	
	54	Wiesener, M.S. et al., "Induction of Endothelial PAS Domain Protein-1 by Hypoxia: Characterization and Comparison with Hypoxia-Inducible Factor-1 $\alpha$ ," <i>Blood</i> , <b>1998</b> , <i>92</i> (7), 2260-2268	
	55	Xia, G. et al., "Regulation of Vascular Endothelial Growth Factor Transcription by Endothelial PAS Domain Protein 1 (EPAS1) and Possible Involvement of EPAS1 in the Angiogenesis of Renal Cell Carcinoma," <i>Cancer</i> , <b>2001</b> , <i>91</i> (8), 1429-1436	
	56	Xia, G. et al., "Positive Expression of HIF-2 $\alpha$ /EPAS1 in Invasive Bladder Cancer," <i>Urology</i> , <b>2002</b> , <i>5</i> , 774-778	
<b>EXAMINER</b>		<b>DATE CONSIDERED</b>	



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office	<b>Docket No.</b> ISPT-1010/ PTS-0070.P1	<b>Application No.</b> 10/719,370
	<b>Applicant</b> Donna T. Ward, et al.	
	<b>Filing Date</b> November 21, 2003	<b>Group</b> Not Yet Assigned
	<b>Confirmation No.</b> Not Yet Assigned	

**U. S. PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Name	Class	Subclass
	57	5,882,914	03/16/99	Semenza	435	252.3
	58	5,695,963	12/09/97	McKnight et al.	435	69.1
	59	6,395,548 B1	05/28/02	Lee et al.	435	455
	60	6,432,927 B1	08/13/02	Gregory et al.	514	44
	61	2003/0045686 A1	03/06/03	Kaelin, Jr. et al.	530	350

**FOREIGN PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Country	Translation	
					YES	NO
	62	WO 00/09657	02/24/00	PCT		
	63	WO 01/62965 A2	08/30/01	PCT		
	64	WO 02/34291 A2	05/02/02	PCT		
	65	WO 02/068466 A2	09/06/02	PCT		
	66	WO 02/086497 A2	10/31/02	PCT		
	67	WO 02/094862 A2	11/28/02	PCT		

<b>EXAMINER</b>	<b>DATE CONSIDERED</b>
-----------------	------------------------